ACS central science

http://pubs.acs.org/journal/acscii

Research Article

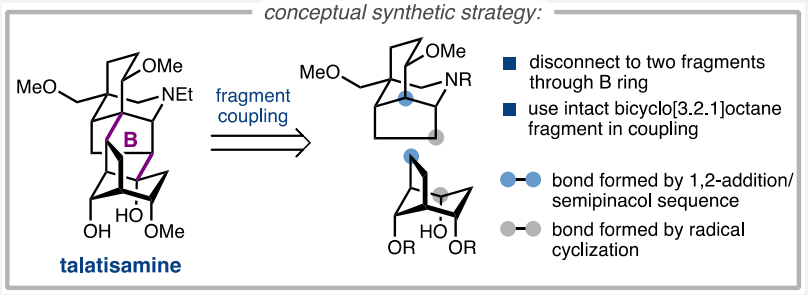
Total Syntheses of the C_{19} Diterpenoid Alkaloids (−)-Talatisamine, (−)-Liljestrandisine, and (−)-Liljestrandinine by a Fragment Coupling Approach

Alice R. Wong, Nicholas J. Fastuca, Victor W. Mak, Jeffrey K. Kerkovius, Susan M. Stevenson, and Sarah E. Reisman*

Cite This: *ACS Cent. Sci.* 2021, 7, 1311−1316

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: The C19 diterpenoid alkaloids (C19 DTAs) are a large family of natural products, many of which modulate the activity of ion channels *in vivo* and are therefore of interest for the study of neurological and cardiovascular diseases. The complex architectures of these molecules continue to challenge the state-of-the art in chemical synthesis, particularly with respect to efficient assembly of their polcyclic ring systems. Here, we report the total syntheses of (−)-talatisamine, (−)-liljestrandisine, and (−)-liljestrandinine, three aconitine-type C19 DTAs, using a fragment coupling strategy. Key to this approach is a 1,2-addition/semipinacol rearrangement sequence which efficiently joins two complex fragments and sets an all-carbon quaternary center.

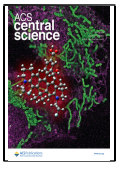
Downloaded via CALIFORNIA INST OF TECHNOLOGY on August 31, 2021 at 19:39:21 (UTC).
See https://pubs.acs.org/sharingguidelines for options on how to legitimately share published articles.

The extracts of the *Aconitum* and *Delphinium* genera of plants have long been used in traditional medicine and as poisons for hunting and battle.[1] The diterpenoid alkaloids are a family of natural products associated with the toxicity of these flowering plants, and many of these compounds exhibit analgesic,[2,3] anti-inflammatory, antihypertensive, and antiarrhythmic[4] properties. (−)-Talatisamine (**1**, Figure 1a) is a representative aconitine-type C19 diterpenoid alkaloid (C19 DTA) that selectively blocks inwardly rectifying K^+ ion channels over Na^+ and Ca^{2+} ion channels in rat neurons,[5] and was found to attenuate neurocytotoxicity induced by β-amyloid oligomers.[6] Minor congeners, such as (−)-liljestrandisine (**2**) and (−)-liljestrandinine (**3**), which vary in the methylation and oxidation pattern, have also been isolated.[7,8]

Biosynthetically, the C19 DTAs arise via the *ent*-atisane cyclase pathway, in which the originally formed denudatine framework (**4**), containing a bicyclo[2.2.2]octane CD ring system, undergoes skeletal rearrangement to the corresponding [3.2.1] CD ring system (**5**) (Figure 1b).[9] The cationic rearrangements involved in the biosynthesis of these natural products have also played an important role in many of the total syntheses of the C19 DTAs, including the pioneering efforts in the 1970s by Wiesner and co-workers,[10−13] and more recent contributions by the Sarpong,[14] Fukuyama,[15] and Inoue laboratories.[16] In each of these approaches, the denudatine-type bicyclo[2.2.2]octane is first assembled by a Diels−Alder reaction, and then rearranged at a late stage to the aconitine-type skeleton. Beyond these bioinspired strategies, a number of other approaches to the C19 DTAs have been disclosed,[17−28] as well as an elegant synthesis by Gin and co-workers of the C18 norditerpenoid alkaloid neofinaconitine (not shown).[29]

As part of a larger program aimed at developing fragment coupling strategies to prepare structurally complex diterpenes,[30] we became interested in the C19 DTAs as synthetic targets. We envisioned that scission of **1** through the C10−C11 and C7−C8 bonds of the central B ring would disconnect the highly bridged hexacyclic framework into two fragments of similar size and complexity (Figure 1b, inset). In the forward direction, the key steps of synthesis would focus on joining the AF ring system with an intact CD bicyclo[3.2.1]octane; we recognized that this approach would hinge on the development

Received: May 5, 2021
Published: July 27, 2021



ACS Publications

© 2021 The Authors. Published by American Chemical Society

https://doi.org/10.1021/acscentsci.1c00540
ACS Cent. Sci. 2021, 7, 1311−1316

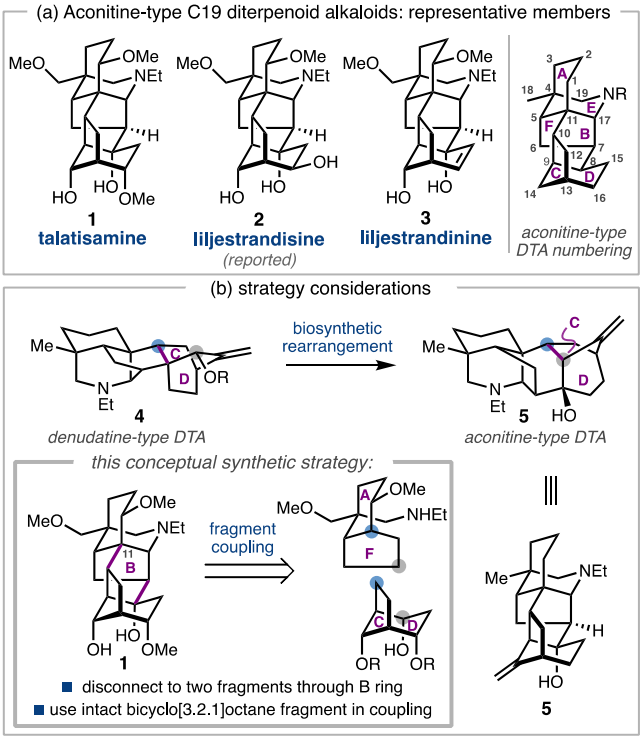


Figure 1. Representative members of the aconitine-type C19 diterpenoid alkaloids and synthetic strategy considerations.

of an efficient method to forge the central C11 quaternary center. In this communication, we report the total syntheses of (−)-talatisamine (**1**), (−)-liljestrandisine (**2**), and (−)-liljestrandinine (**3**), which feature a 1,2-addition/semipinacol rearrangement as the key fragment coupling tactic. These efforts have also resulted in a correction to the original structure assignment of (−)-liljestrandisine (**2**).[8]

Given the conceptual strategy outlined in Figure 1, we developed the retrosynthesis of **1** shown in Figure 2. We sought to simplify **1** to amine **6** by disconnection of the C17−N and C7−C8 bonds; in the forward sense, we envisioned use of an *N*-centered radical cascade to close the E and B rings in a single transformation. Amine **6** was expected to be accessible from the corresponding ketone, **7**, via a series of reductions and amination at C19. To join the AF and CD rings, we designed a two-step sequence involving (1) 1,2-addition of an organometallic reagent derived from alkenyl bromide **10** to epoxy ketone **9**, and (2) semipinacol rearrangement of **8**, in which the strain-release of the epoxide opening would serve as a thermodynamic driving force for formation of the hindered C11 quaternary center. Although the semipinacol rearrangement has been used in many total syntheses,[31] it is not typically employed as part of a fragment coupling strategy; we anticipated that this approach could highlight the utility of this overall two-step tactic for building polycyclic systems. Finally, epoxyketone **9** and alkenyl bromide **10** would be prepared from the simple starting materials cyclopent-2-en-1-one (**11**) and phenol (**12**), respectively. It was expected that this approach to (−)-**1** would also provide access to (−)-(**2**) and (−)-(**3**) through adjustments to the final sequence of reduction steps.

The synthesis of epoxy-ketone **9** began with the asymmetric Michael addition of dimethyl malonate (**13**) to **11** using the chiral gallium−sodium−BINOL catalyst ((*S*)-**12**) developed by Shibasaki and co-workers,[32−34] which furnished cyclopentanone **14** in 88% yield and 91% enantiomeric excess (ee) (Scheme 1a). The ketone of **14** was protected as the dioxolane to give **15**, which was alkylated with **16** and subjected to HCl in refluxing acetone to yield hydrindenone **17** in 67% yield over two steps. The required epoxide was accessed by first converting **17** to the bromohydrin, which was isolated as a single diastereomer after trituration.[35] Treatment with triethylamine followed by recrystallization furnished epoxyketone **9** in 62% yield (two steps) and >99% ee.

The synthesis of the bicyclo[3.2.1]octadiene **10** commenced with a diastereoselective intramolecular *meta*-photocycloaddition of aryl ether **18** following the protocol reported by Sugimura (Scheme 1b).[36,37] Epoxidation of **19** and treatment with HCl resulted in Grob-type fragmentation to afford **20**. Luche reduction of **20** afforded the diaxial 1,3-diol, which was protected as a siliconide (**21**). The chiral auxiliary was cleaved by oxidation of the secondary alcohol under conditions reported by Stahl and co-workers[38] followed by addition of K_2CO_3 and methanol to liberate alcohol **22**. Upon oxidation to the ketone and conversion to enol triflate **23**, alkenyl bromide **10** was generated using a Ni-catalyzed enol-triflate halogenation developed in our laboratory.[39]

Having prepared **9** and **10**, we investigated the key fragment coupling step (Scheme 2). To this end, alkenyl bromide **10** was submitted to lithium-halogen exchange and the corresponding alkenyllithium was added to epoxyketone **9** at −94 °C to give the 1,2-addition product which, after quenching with TMSCl, was isolated as silyl ether **8** in 77% yield as a single diastereomer. To our delight, treatment of **8** with catalytic $TMSNTf_2$ (10 mol %) at −78 °C smoothly effected the desired semipinacol rearrangement. Under these conditions, ketone **7** is isolated in 97% yield on a 4 g scale. This remarkable two-step process forges the key C10−C11 bond and highlights the power of the 1,2-addition/semipinacol

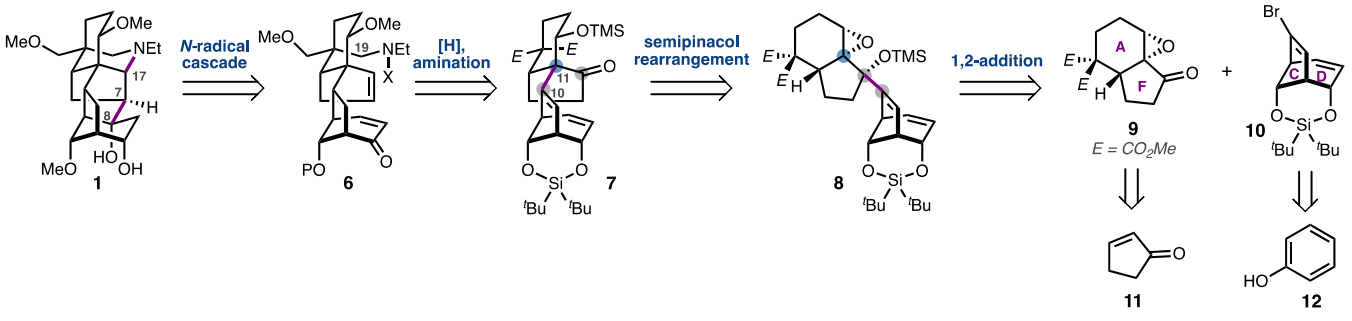
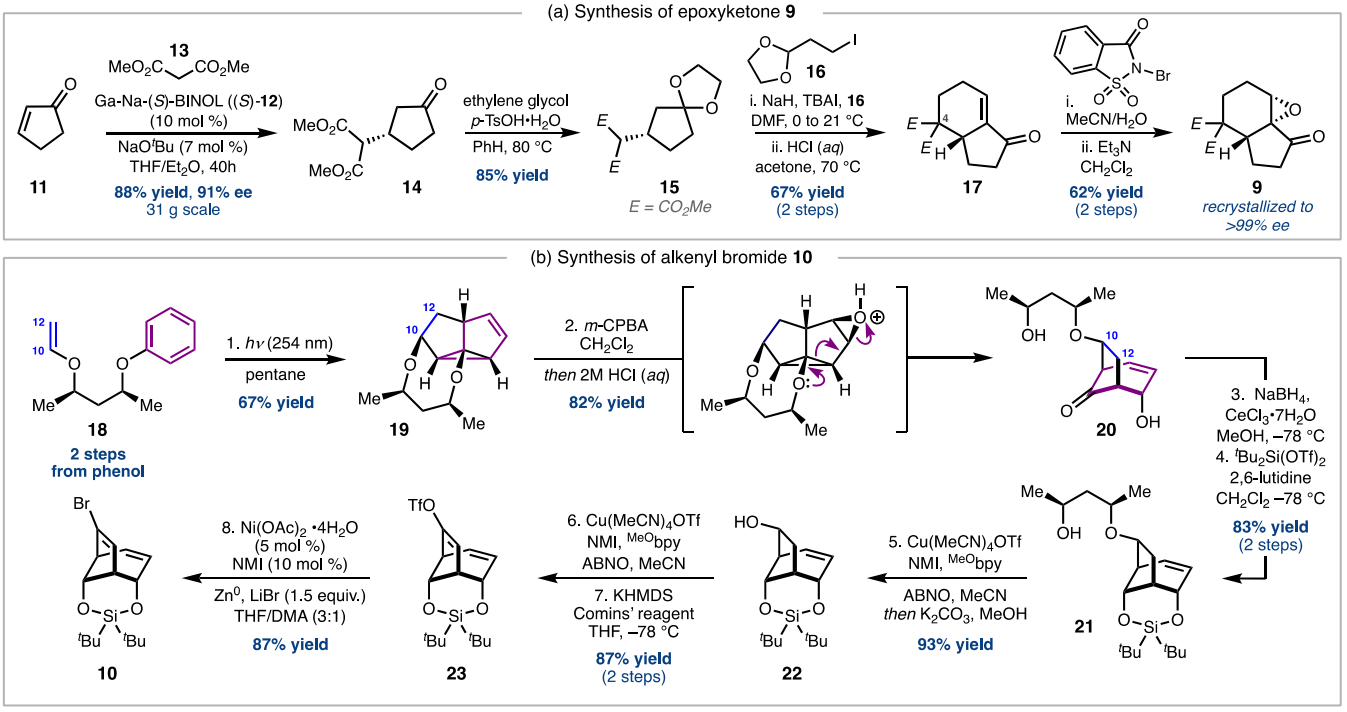


Figure 2. Retrosynthetic analysis of (−)-talatisamine (**1**).

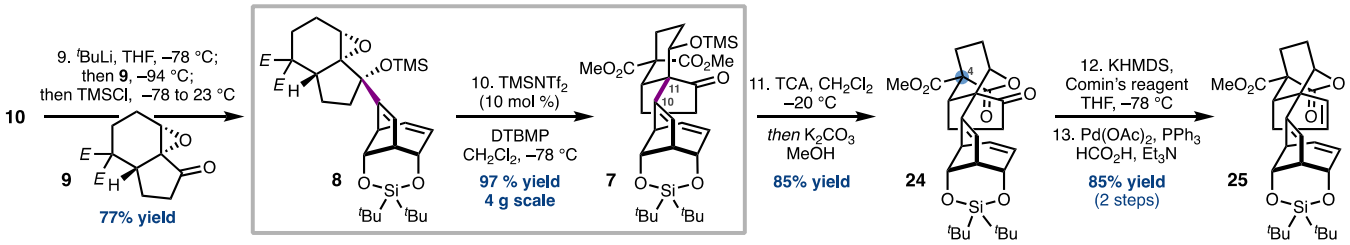
https://doi.org/10.1021/acscentsci.1c00540
ACS Cent. Sci. 2021, 7, 1311−1316

Scheme 1. Enantioselective Synthesis of Epoxyketone 9 and Alkenyl Bromide 10[a]



[a]Reagent abbreviations: *m*-CPBA, *meta*-chloroperbenzoic acid; NMI, *N*-methylimidazole; ABNO, 9-azabicyclo[3.3.1]nonane *N*-oxyl radical; ^{MeO}bpy, 4,4′-dimethoxy-2-2′-bipyridine.

Scheme 2. Synthesis of Lactone 25 Using a 1,2-Addition/Semipinacol Rearrangement as the Key Fragment Coupling Tactic[a]



[a]Reagent abbreviations: TMSCl, trimethylsilyl chloride; TMSNTf$_2$, *N*-(trimethylsilyl)bis(trifluoromethanesulfonyl)imide; DTBMP, 2,6-di-*tert*-butyl-4-methylpyridine; TCA, trichloroacetic acid; KHMDS, potassium bis(trimethylsilyl)amide.

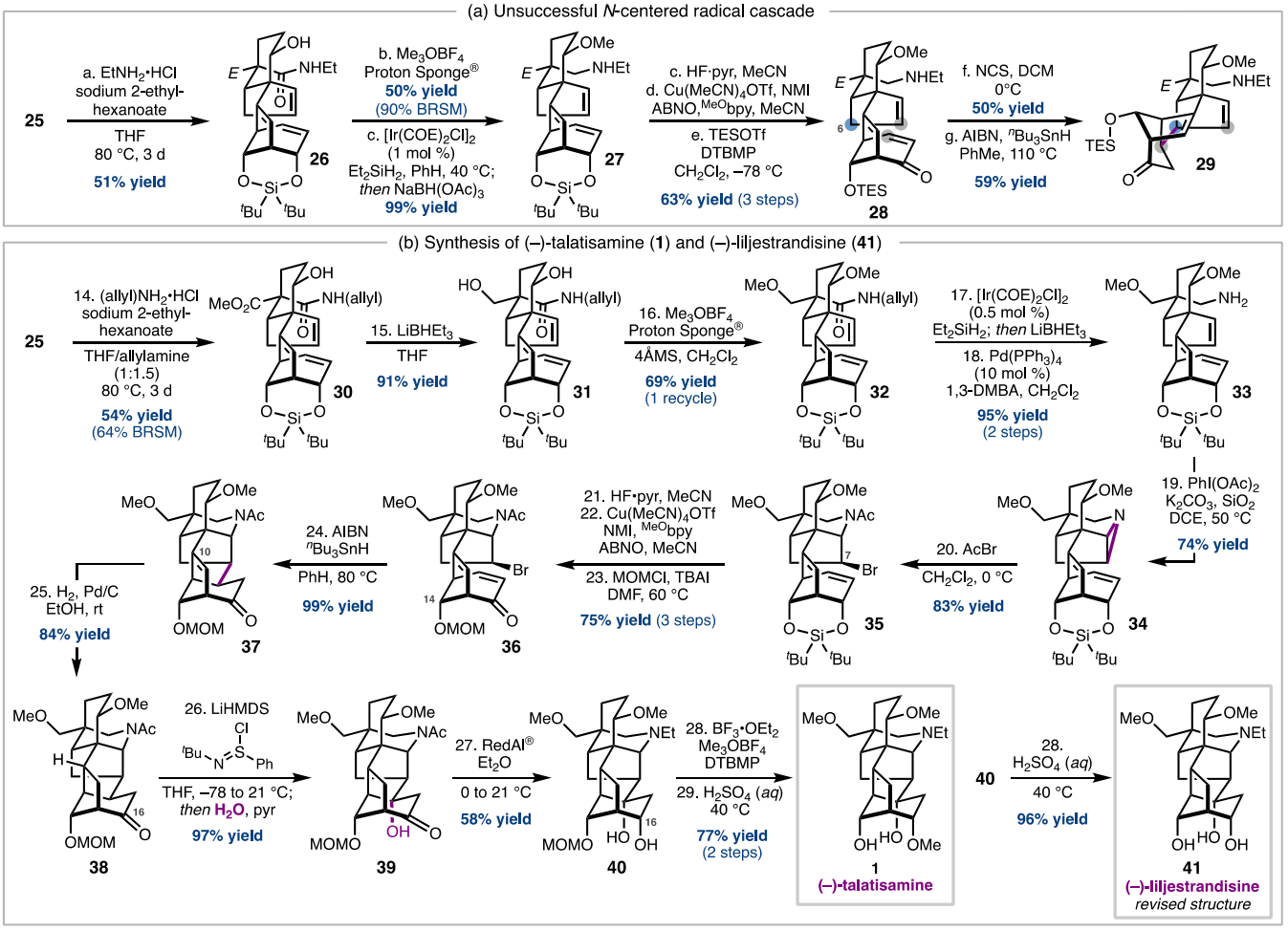
rearrangement as a fragment coupling tactic for complex polycycles. Deprotection of the TMS-ether enabled cyclization to form the strained lactone **24**, thereby differentiating the two esters at C4. Conversion of the ketone to the enol triflate and Pd-catalyzed reduction afforded olefin **25** in excellent yield.

At this stage, we turned our attention to formation of the E and B rings by the proposed *N*-centered radical cascade (Scheme 3a). Access to the aminyl radical precursor required selective aminolysis of lactone **25** with ethylamine to give amide **26**. The secondary alcohol of **26** was methylated with trimethyloxonium tetrafluoroborate (Me_3OBF_4). Selective reduction of the C19-amide to the imine was achieved using the Ir-catalyzed hydrosilylation developed by Brookhart, and further reduction with $NaBH(OAc)_3$ afforded amine **27** in excellent yield.[40] A three step sequence involving desilylation, chemoselective oxidation of the allylic alcohol, and protection of the remaining secondary alcohol as the triethylsilyl ether gave CD enone **28**. Finally, treatment of **28** with *N*-chlorosuccinimide furnished the corresponding *N*-chloroamine (structure not shown). Unfortunately, efforts to effect the *N*-centered radical cascade under a number of conditions, including $^nBu_3SnH$/AIBN,[41−46] failed to give the desired product. Instead, under these conditions, the major product was **29**, presumably resulting from a 1,5-hydrogen atom transfer at C6 followed by 1,4-addition to the enone.

Having encountered challenges in forming the B and E rings through a cascade reaction, we pursued formation of the C−N and C−C bonds in a stepwise approach (Scheme 3b). To this end, aminolysis of lactone **25** with *N*-allylamine furnished amide **30** in 54% yield (64% BRSM). Reduction of the methyl ester followed by bis-methylation with Me_3OBF_4 delivered **32**. The C19 amide was reduced to the amine using conditions analogous to those employed en route to **27**; in this system, the Ir conditions proved uniquely effective at reducing the amide without also reducing the *N*-allyl group. The *N*-allyl substituent was cleaved under Pd-catalyzed conditions to give **33**.[47] Cyclization to form the E-ring piperidine was achieved by intramolecular aziridination,[28] providing **34** in 74% yield. Treatment of aziridine **34** with acetyl bromide delivered alkyl bromide **35** in 83% yield. Notably, this transformation installed

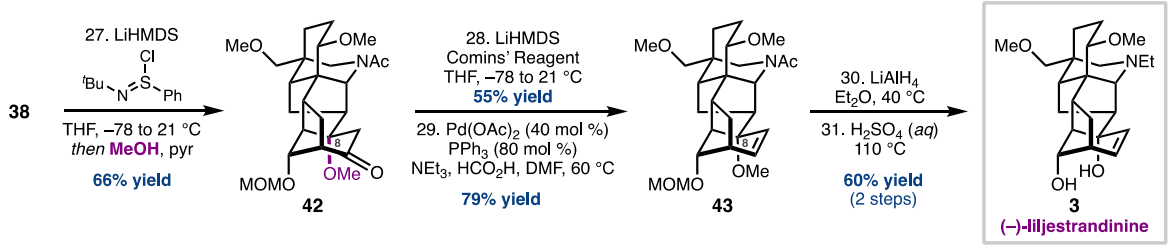
https://doi.org/10.1021/acscentsci.1c00540
ACS Cent. Sci. 2021, 7, 1311−1316

Scheme 3. (a) Attempted *N*-Centered Radical Cascade Approach to (−)-1; (b) Completion of the Synthesis of (−)-Talatisamine (1) and Structural Revision of (−)-Liljestrandisine (41)[a]



[a]Reagent abbreviations: Proton Sponge, 1-8-bis(dimethylamino)naphthalene; NMI, *N*-methylimidazole; ABNO, 9-azabicyclo[3.3.1]nonane *N*-oxyl radical; ^{MeO}bpy, 4,4′-dimethoxy-2-2′-bipyridine; TESOTf, triethylsilyl trifluoromethanesulfonate; DTBMP, 2,6-di-*tert*-butyl-4-methylpyridine; NCS, *N*-chlorosuccinimide; AIBN, 2,2′-azobis(2-methylpropionitrile); 1,3-DMBA, 1,3-dimethylbarbituric acid; MOMCl, chloromethyl methyl ether; TBAI, tetrabutylammonium iodide; LiHMDS, lithium bis(trimethylsilyl)amide; pyr, pyridine; RedAl, sodium bis(2-methoxyethoxy) aluminum hydride.

Scheme 4. Completion of the Synthesis of (−)-Liljestrandinine (3)[a]



[a]Reagent abbreviations: LiHMDS, lithium bis(trimethylsilyl)amide.

the C7 radical precursor and also introduced the two carbons of the *N*-ethyl substituent in the form of an acetamide. In analogy to **27**, siliconide **35** was elaborated to **36** by desilylation, oxidation, and MOM-protection of the C14 alcohol. We were pleased to find that heating **36** with ^{n}Bu$_3$SnH and AIBN resulted in the desired radical cyclization,[29] closing the B ring and delivering hexacyclic ketone **37** in 99% yield.

To complete the syntheses of (−)-**1** and (−)-**2**, hydrogenation of the strained C10−C12 alkene was followed by Mukaiyama dehydrogenation of the C16 ketone. Presumably, the strained bridgehead enone that initially forms undergoes oxy-conjugate addition upon addition of water and pyridine.[29,48] Treatment of **39** with Red-Al reduced the acetamide to the *N*-ethylamine and the ketone to the alcohol, delivering **40** with good selectivity for the axial diastereomer. Selective

https://doi.org/10.1021/acscentsci.1c00540
ACS Cent. Sci. 2021, 7, 1311−1316

methylation of the C16 alcohol of **40** followed by MOM deprotection afforded (−)-talatisamine ((−)-**1**) in 77% yield over the final two steps. Alternatively, treatment of **40** directly with aqueous H_2SO_4 gave triol **41**, and the ^1H and ^{13}C NMR data for which were consistent with that reported for (−)-liljestrandisine. Indeed, when the equatorial C16 epimer of **40** (not shown) was elaborated to compound **2** (Figure 1)—the originally proposed structure for (−)-liljestrandisine[8]—the ^1H and ^{13}C NMR did not match the literature data. On the basis of this synthetic work, we propose that the structure of (−)-liljestrandisine should be revised to **41**.

The related target (−)-liljestrandinine (**3**) could be prepared from **38** by a slightly modified sequence. Dehydrogenation of **38** followed by addition of methanol and pyridine delivered C8 methyl ether **42** in 66% yield (Scheme 4). Conversion of ketone **42** to the enol triflate followed by Pd-catalyzed reduction gave alkene **43**. Amide reduction with lithium aluminum hydride followed by MOM deprotection and S_N1 hydrolysis of the C8 methoxy group delivered (−)-**3**.

In conclusion, the C19 DTAs (−)-talatisamine, (−)-liljestrandisine, and (−)-liljestrandinine have been prepared in 31, 30, and 33 steps in the longest linear sequence, respectively, from phenol (**12**) (37, 36, and 39 steps total). Our synthetic approach leverages a 1,2-addition/semipinacol rearrangement sequence as a powerful tactic for the coupling of complex ring-containing fragments. Although efforts to use an *N*-centered radical cascade to simultaneously form the E and B rings were unsuccessful, the general bond constructions could be executed in a stepwise fashion by way of an intramolecular aziridination and subsequent radical cyclization. These studies highlight the 6-*exo*-trig cyclization of *N*-centered radicals as a prime area for future reaction development. Efforts to apply similar fragment coupling strategies in combination with radical cascade reactions to other DTAs are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications Web site. (pdf). The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscentsci.1c00540.

Experimental procedures, characterization data (^1H and ^{13}C NMR, HRMS, FTIR) for all new compounds (PDF)

CIF files (ZIP)

■ AUTHOR INFORMATION

Corresponding Author

Sarah E. Reisman − *The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States;* orcid.org/0000-0001-8244-9300; Email: reisman@caltech.edu

Authors

Alice R. Wong − *The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States;* orcid.org/0000-0002-1038-4453

Nicholas J. Fastuca − *The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States*

Victor W. Mak − *The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States*

Jeffrey K. Kerkovius − *The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States*

Susan M. Stevenson − *The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscentsci.1c00540

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Dr. Scott Virgil and the Caltech Center for Catalysis and Chemical Synthesis are gratefully acknowledged for access to analytical equipment. Fellowship support was provided by the NSF (V.W.M., A.R.W., Grant No. DGE-1144469), Natural Sciences and Engineering Research Council of Canada (J.K.K., Grant No. 532535), and the NIH (F32 GM122386 to S.M.S. and T32 GM07616 to N.J.F.). S.E.R. is a Heritage Medical Research Institute Investigator and acknowledges financial support from the NIH (R35GM118191).

■ REFERENCES

(1) Sung, Y. *Chinese Technology in the Seventeenth Century*; Sun, E.-T. Z., Sun, S.-C., Translators; Pennsylvania State University: University Park, 1966.

(2) Friese, J.; Gleitz, J.; Gutser, U. T; Heubach, J. F; Matthiesen, T.; Wilffert, B.; Selve, N. Aconitum Sp. Alkaloids: The Modulation of Voltage-Dependent Na^+ Channels, Toxicity and Antinociceptive Properties. *Eur. J. Pharmacol.* **1997**, *337*, 165−174.

(3) Gutser, U. T.; Friese, J.; Heubach, J. F.; Matthiesen, T.; Selve, N.; Wilffert, B.; Gleitz, J. Mode of Antinociceptive and Toxic Action of Alkaloids of Aconitum Spec. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1997**, *357*, 39−48.

(4) Vakhitova, Yu. V.; Farafontova, E. I.; Khisamutdinova, R. Yu; Yunusov, V. M.; Tsypysheva, I. P.; Yunusov, M. S. A Study of the Mechanism of the Antiarrhythmic Action of Allapinin. *Russ. J. Bioorg. Chem.* **2013**, *39*, 92−101.

(5) Song, M.-K.; Liu, H.; Jiang, H.-L.; Yue, J.-M.; Hu, G.-Y.; Chen, H.-Z. Discovery of Talatisamine as a Novel Specific Blocker for the Delayed Rectifier K^+ Channels in Rat Hippocampal Neurons. *Neuroscience* **2008**, *155*, 469−475.

(6) Wang, Y.; Song, M.; Hou, L.; Yu, Z.; Chen, H. The Newly Identified K^+ Channel Blocker Talatisamine Attenuates beta-amyloid Oligomers Induced Neurotoxicity in Cultured Cortical Neurons. *Neurosci. Lett.* **2012**, *518*, 122−127.

(7) Xie, G. B.; Chen, Q. H.; Chen, D. L.; Jian, X. X.; Wang, F. P. New C19-Diterpenoid Alkaloids from *Aconitum liljestrandii*. *Heterocycles* **2003**, *60*, 631−636.

(8) Xie, G.-B.; Wang, F.-P. Structure of Liljestrandisine—a New C19 Diterpenoid Alkaloid from *Aconitum liljestrandii*. *Chem. J. Chin. Univ.* **2004**, *25*, 482−483.

(9) Wang, F.-P.; Chen, Q.-H. The C19-Diterpenoid Alkaloids. In *The Alkaloids: Chemistry and Biology*; Elsevier, 2010; Vol. *69*, pp 1−577.
(10) Wiesner, K.; Ho, P.-T.; Jain, R. C.; Lee, S. F.; Oida, S.; Philipp, A. Synthesis and Rearrangement Control of Substituted Benzobicycloheptane Aziridines. *Can. J. Chem.* **1973**, *51*, 1448−1457.
(11) Wiesner, K.; Ho, P.-T.; Chang, D.; Lam, Y. K.; Pan, C. S. J.; Ren, W. Y. The Synthesis of Songorine: A Simplified Synthesis of the Aromatic Intermediate. *Can. J. Chem.* **1973**, *51*, 3978−3988.
(12) Wiesner, K.; Tsai, T. Y. R.; Huber, K.; Bolton, S. E.; Vlahov, R. Total Synthesis of Talatisamine, a Delphinine Type Alkaloid. *J. Am. Chem. Soc.* **1974**, *96*, 4990−4992.
(13) Wiesner, K.; Tsai, T. Y. R.; Nambiar, K. P. A New Stereospecific Total Synthesis of Chasmanine and 13-Desoxydelphonine. *Can. J. Chem.* **1978**, *56*, 1451−1454.
(14) Marth, C. J.; Gallego, G. M.; Lee, J. C.; Lebold, T. P.; Kulyk, S.; Kou, K. G. M.; Qin, J.; Lilien, R.; Sarpong, R. Network-Analysis-Guided Synthesis of Weisaconitine D and Liljestrandinine. *Nature* **2015**, *528*, 493−498.
(15) Nishiyama, Y.; Yokoshima, S.; Fukuyama, T. Total Synthesis of (−)-Cardiopetaline. *Org. Lett.* **2016**, *18*, 2359−2362.
(16) Kamakura, D.; Todoroki, H.; Urabe, D.; Hagiwara, K.; Inoue, M. Total Synthesis of Talatisamine. *Angew. Chem., Int. Ed.* **2020**, *59*, 479−486.
(17) Additional approaches to C19 DTAs listed here: Shishido, K.; Hiroya, K.; Fukumoto, K.; Kametani, T. An Efficient and Highly Regioselective Intramolecular Mannich-Type Reaction: A Construction of the AEF Ring System of Aconitine-Type Diterpene Alkaloids. *Tetrahedron Lett.* **1986**, *27*, 1167−1170.
(18) Kraus, G. A.; Andersh, B.; Su, Q.; Shi, J. *Tetrahedron Lett.* **1993**, *34*, 1741−1744.
(19) Baillie, L. C.; Bearder, J. R.; Li, W.-S.; Sherringham, J. A.; Whiting, D. A. Studies into the Synthesis of a Sub-Unit of the Neurotoxic Alkaloid Methyllycaconitine. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4047−4056.
(20) Taber, D. F.; Liang, J.-L.; Chen, B.; Cai, L. A Model Study toward the Total Synthesis of *N* -Deacetyllappaconitine. *J. Org. Chem.* **2005**, *70*, 8739−8742.
(21) Kraus, G. A.; Kesavan, S. Preparation of Advanced Intermediates for the Synthesis of Both Methyllycaconitine and Racemulsonine via a Common Intermediate. *Tetrahedron Lett.* **2005**, *46*, 1111−1113.
(22) Conrad, R. M.; Du Bois, J. C−H Amination in Synthesis: An Approach to the Assembly of the B/C/D Ring System of Aconitine. *Org. Lett.* **2007**, *9*, 5465−5468.
(23) Yang, Z.-K.; Chen, Q.-H.; Wang, F.-P. Construction of AE Ring System for the C19-Diterpenoid Alkaloids with a 5*β*-Hydroxyl Group. *Tetrahedron* **2011**, *67*, 4192−4195.
(24) Liu, Z.-G.; Xu, L.; Chen, Q.-H.; Wang, F.-P. Construction of A/E/F Ring Systems of C19-Diterpenoid Alkaloids with Both C-1 and C-6 Oxygen Functions. *Tetrahedron* **2012**, *68*, 159−165.
(25) Goodall, K. J.; Brimble, M. A.; Barker, D. A Tandem Diels−Alder/Mannich Approach to the Synthesis of AE and ABE Ring Analogues of Delphinium Alkaloids. *Tetrahedron* **2012**, *68*, 5759−5778.
(26) Cheng, H.; Zeng, F.-H.; Ma, D.; Jiang, M.-L.; Xu, L.; Wang, F.-P. Expedient Construction of the ABEF Azatetracyclic Ring Systems of Lycoctonine-Type and 7,17- *Seco* -Type C $_{19}$ -Diterpenoid Alkaloids. *Org. Lett.* **2014**, *16*, 2299−2301.
(27) Tabuchi, T.; Urabe, D.; Inoue, M. Construction of the Fused Pentacycle of Talatisamine via a Combination of Radical and Cationic Cyclizations. *J. Org. Chem.* **2016**, *81*, 10204−10213.
(28) Liu, Z.-G.; Cheng, H.; Ge, M.-J.; Xu, L.; Wang, F.-P. PIDA-Promoted Intramolecular Transannular Aziridination to Synthesize Bridged Azatricyclic Amines Related to Methyllycaconitine. *Tetrahedron* **2013**, *69*, 5431−5437.
(29) Total Synthesis, Relay Synthesis and Structural Confirmation of the C18-Norditerpenoid Alkaloid Neofinaconitine. Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313−14320.
(30) Dibrell, S. E.; Tao, Y.; Reisman, S. E. Synthesis of Complex Diterpenes: Strategies Guided by Oxidation Pattern Analysis. *Acc. Chem. Res.* **2021**, *54*, 1360−1373.
(31) Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. Semipinacol Rearrangement in Natural Product Synthesis. *Chem. Rev.* **2011**, *111*, 7523−7556.
(32) See the Supporting Information for catalyst structure.
(33) Arai, T.; Yamada, Y. M. A.; Yamamoto, N.; Sasai, H.; Shibasaki, M. Self-Assembly of Heterobimetallic Complexes and Reactive Nucleophiles: A General Strategy for the Activation of Asymmetric Reactions Promoted by Heterobimetallic Catalysts. *Chem. - Eur. J.* **1996**, *2*, 1368−1372.
(34) Fastuca, N. J.; Wong, A. R.; Mak, V. W.; Reisman, S. E. Asymmetric Michael Addition of Dimethyl Malonate to 2-Cyclopenten-1-one Catalyzed by a Heterobimetallic Complex. *Org. Synth.* **2020**, *97*, 327−338.
(35) Crude reaction mixture shows 3:1 d.r. by ^{1}H NMR.
(36) Hagiya, K.; Yamasaki, A.; Okuyama, T.; Sugimura, T. Asymmetric Meta-Arene−Alkene Photocycloaddition Controlled by a 2,4-Pentanediol Tether. *Tetrahedron: Asymmetry* **2004**, *15*, 1409−1417.
(37) Sugimura, T.; Yamasaki, A.; Okuyama, T. Stereocontrolled Intramolecular Meta-Arene−Alkene Photocycloaddition Reactions Using Chiral Tethers: Efficiency of the Tether Derived from 2,4-Pentanediol. *Tetrahedron: Asymmetry* **2005**, *16*, 675−683.
(38) Steves, J. E.; Stahl, S. S. Copper(I)/ABNO-Catalyzed Aerobic Alcohol Oxidation: Alleviating Steric and Electronic Constraints of Cu/TEMPO Catalyst Systems. *J. Am. Chem. Soc.* **2013**, *135*, 15742−15745.
(39) Hofstra, J. L.; Poremba, K. E.; Shimozono, A. M.; Reisman, S. E. Ni-Catalyzed Conversion of Enol Triflates to Alkenyl Halides. *Angew. Chem., Int. Ed.* **2019**, *58*, 14901−14905.
(40) Cheng, C.; Brookhart, M. Iridium-Catalyzed Reduction of Secondary Amides to Secondary Amines and Imines by Diethylsilane. *J. Am. Chem. Soc.* **2012**, *134*, 11304−11307.
(41) We also investigated the Cu-catalyzed cyclization of the *N*-chloroamine, as well as the cyclizations of aminium radical cations derived from **28** and related amidyl radical cyclizations.
(42) Miller, D. C.; Ganley, J. M.; Musacchio, A. J.; Sherwood, T. S.; Ewing, W. R.; Knowles, R. R. Anti-Markovnikov Hydroamination of Unactivated Alkenes with Primary Alkyl Amines. *J. Am. Chem. Soc.* **2019**, *141*, 16590−16594.
(43) Nguyen, S. T.; Zhu, Q.; Knowles, R. R. PCET-Enabled Olefin Hydroamidation Reactions with *N*-alkyl amides. *ACS Catal.* **2019**, *9*, 4502−4507.
(44) Musacchio, A. J.; Lainhart, B. C.; Zhang, X.; Naguib, S. G.; Sherwood, T. C.; Knowles, R. R. Catalytic Intermolecular Hydroaminations of Unactivated Olefins with Secondary Alkyl Amines. *Science* **2017**, *355*, 727−730.
(45) Stella, L.; Raynier, B.; Surzur, J.-M. Synthesis of 2-Methyl-6,7-Benzomorphane via Radical Cyclisation. *Tetrahedron Lett.* **1977**, *18*, 2721−2724.
(46) Heuger, G.; Kalsow, S.; Göttlich, R. Copper(I) Catalysts for the Stereoselective Addition of *N*-Chloroamines to Double Bonds: A Diastereoselective Radical Cyclisation. *Eur. J. Org. Chem.* **2002**, *2002*, 1848−1854.
(47) Garro-Helion, F.; Merzouk, A.; Guibe, F. Mild and Selective Palladium(0)-Catalyzed Deallylation of Allylic Amines. Allylamine and Diallylamine as Very Convenient Ammonia Equivalents for the Synthesis of Primary Amines. *J. Org. Chem.* **1993**, *58*, 6109−6113.
(48) Mukaiyama, T.; Matsuo, J.; Kitagawa, H. A New and One-Pot Synthesis of *α*,*β*-Unsaturated Ketones by Dehydrogenation of Various Ketones with *N-Tert* -Butyl Phenylsulfinimidoyl Chloride. *Chem. Lett.* **2000**, *29*, 1250−1251.

https://doi.org/10.1021/acscentsci.1c00540
ACS Cent. Sci. 2021, 7, 1311−1316